

*Corridor Consult*

# Calcific Uremic Arteriopathy: An Underrecognized Entity

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## Abstract

Calcific uremic arteriopathy (CUA), or calciphylaxis, is an uncommon and underrecognized disease that often occurs in the setting of chronic kidney disease or end-stage renal disease. It is characterized by small-vessel calcification, although many times it is associated with normal serum levels of calcium, phosphorus, and parathyroid hormone. The lesions appear as necrotic eschars, ulcerations, indurated nodules, and dry gangrene and are usually very painful. Diagnosis is based on clinical judgment and recognition of characteristic skin lesions. Biopsy can be performed but may be complicated by poor wound healing. Treatment of CUA involves rigorous wound care, strict control of mineral metabolism with avoidance of calcium and vitamin D analogs, and pain control. Other treatment options include sodium thio-sulfate, hyperbaric oxygen therapy, daily hemodialysis using low-calcium dialysate, and bisphosphonates. Even with treatment, CUA is associated with significant morbidity and mortality. The patient in the case reported here had characteristic skin lesions and several risk factors for CUA, but diagnosis was delayed.

## Case Presentation

A Vietnamese woman, age 67 years, with end-stage renal disease (ESRD) due to systemic lupus erythematosus currently receives short daily home hemodialysis (SDHD), using the NxStage system one machine (NxStage Medical, Inc, Lawrence, MA, USA) with the assistance of her husband. She uses a right internal jugular (RIJ) tunneled catheter because of a previous rupture of an arteriovenous fistula, complicated by a three-week stay in an intensive care unit. Her other medical problems include hypertension, pancytopenia (related to systemic lupus erythematosus), secondary hyperparathyroidism, hyperlipidemia, and asthma.

Even though the patient took calcitriol (1,25-dihydroxyvitamin D) and phosphate binders, her parathyroid hormone level had continued to rise during the preceding year (>1000 pg/mL). She has followed instructions regarding the use of sevelamer carbonate

as a phosphate binder, and her serum phosphorus level was generally controlled. After she developed hypercalcemia, she was given cinacalcet (an oral calcimimetic agent used to suppress the parathyroid gland). She developed severe nausea and vomiting, so the cinacalcet was discontinued. The patient was subsequently referred to general surgery for parathyroidectomy; however, surgery was not performed, owing to the patient's overall condition and because she lacked symptoms such as bone pain or pruritus.

The patient later experienced poor blood flow in her RIJ catheter and was referred to interventional radiology for catheter change via a guidewire. She received a platelet transfusion just before the procedure (2 units), as recommended by her hematologist. The catheter exchange was successful, but she experienced persistent bleeding from the tunnel track and developed a hematoma after the procedure. Bleeding was controlled with lidocaine 1% and epinephrine (1:100,000, 10 mL) and Gelfoam packing. She continued to have persistent bleeding as well as elevated blood pressure, so she was admitted to the hospital for overnight observation. Her blood pressure was controlled, and she received DDAVP (1-deamino-8-D-arginine vasopressin, or desmopressin) for the bleeding. She was discharged to her home, but on the following day, she developed swelling at the catheter site during SDHD treatment, and her husband called paramedics.

The patient was admitted to a hospital not affiliated with Kaiser Permanente, where she was evaluated by a vascular surgeon. Two units of packed red blood cells and several units of fresh-frozen plasma were administered, and then her chest hematoma was evacuated. A nontunneled femoral catheter was placed for hemodialysis, though the patient's RIJ catheter remained in position. The patient's condition was eventually stabilized, and she was transferred to the Los Angeles County Medical Center after approximately one week.

At the time of transfer, the patient's chest wall had a large area of eschar over the right side, with surrounding erythema and purulent drainage. Because of severe pain, the patient could not move her right arm. She was treated with intravenous clindamycin and

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vancomycin and oral ciprofloxacin. Repeat blood and wound cultures were obtained and the General Surgery Department was consulted for possible wound débridement. Hydromorphone was prescribed for pain control.

After consideration of the patient's medical history and examination of the wound, the treating nephrologist developed a working diagnosis of calcific uremic arteriopathy (CUA), or calciphylaxis. A bone scan revealed a focal area of increased uptake in the soft tissue of the right superior lateral area of the chest consistent with CUA. A skin biopsy was not performed, because there were concerns about poor wound healing.

**Background**

CUA is a rare condition characterized by small-vessel calcification, thrombosis, and skin and soft-tissue necrosis.<sup>1</sup> The condition occurs primarily in patients with ESRD but has also been described in patients without chronic kidney disease.<sup>2</sup> Reported risk factors for CUA are listed in Table 1. The pathogenesis of CUA is complex, however, and many times CUA is associated with normal serum levels of calcium, phosphorus, and parathyroid hormone. Recent evidence suggests that vascular calcification is not a passive process of mineral deposition but rather an active cell-mediated process resembling osteogenesis.<sup>3</sup> Much of the current knowledge regarding CUA is based on small retrospective case series and reports. Conflicting reports, especially regarding risk factors for CUA, are common. CUA remains poorly understood and is associated with high morbidity and mortality.

**Diagnosis**

CUA should be considered when at-risk patients (especially those with ESRD) develop characteristic skin

lesions. The lesions appear as necrotic eschars, ulcerations, indurated nodules, and dry gangrene and are usually very painful.<sup>4</sup> Lesions occur frequently in the lower extremities,<sup>1</sup> particularly the distal portion,<sup>5</sup> but have also been described on the abdomen,<sup>6</sup> the penis,<sup>7</sup> the breast,<sup>8</sup> and the upper extremities.<sup>9</sup> Lesions may occur after skin trauma.

Diagnosis can be confirmed by biopsy of a suspicious area; however, poor wound healing and infection may occur after the procedure. A bone scan can aid in the diagnosis of CUA and can be used to assess response to treatment during follow-up care.<sup>10</sup>

**Treatment**

Treatment of CUA involves rigorous wound care,<sup>5</sup> strict control of mineral metabolism with avoidance of calcium and vitamin D analogs,<sup>11</sup> adequate dialysis using low-calcium dialysate, and pain control. Sodium thiosulfate, an antioxidant and cation chelator, has been successfully used, according to several reports.<sup>12-14</sup> Parathyroidectomy has been advocated by some researchers for wound healing,<sup>15</sup> but others suggest that surgery is ineffective and does not prolong survival.<sup>16</sup> Newer agents, such as cinacalcet, have been used to suppress parathyroid hormone, either alone or in combination with paracalcitol.<sup>17,18</sup> Bisphosphonates have also been used to suppress osteogenesis in CUA.<sup>19</sup> Though not widely available, hyperbaric oxygen chambers have been used with some success to treat CUA.<sup>20</sup>

**Case Outcome**

When CUA was suspected in our patient, calcitriol was immediately discontinued, and she was given low-calcium dialysate (2.0 mEq/L). Even after these measures, her serum calcium level became elevated during hospitalization, probably due to immobilization. Sodium thiosulfate 25% (25 g) was administered daily as an intravenous infusion. A culture obtained from the patient's chest wound grew *Pseudomonas aeruginosa*, which was treated with oral ciprofloxacin for a total of three weeks.

The patient was eventually discharged to her home and resumed SDHD using her RIJ catheter, despite the surrounding wound. Her husband administered sodium thiosulfate after each dialysis treatment using a peripherally inserted central catheter. She was seen in the home dialysis clinic approximately two weeks after hospital discharge, and her wound demonstrated growth of granulation tissue (Figure 1). At a follow-up examination, she reported nausea and anorexia, and her dose of sodium thiosulfate was decreased to 18 g. Her symptoms continued to decrease, and her wound continued to heal; the patient discontinued sodium

**Table 1. Potential risk factors for calcific uremic arteriopathy**

Elevated calcium phosphorus product level
Calcium ingestion (especially in the form of phosphate binders)
Hyperphosphatemia
Vitamin D ingestion
Elevated serum levels of alkaline phosphatase
Elevated serum levels of aluminum
Corticosteroid use
Warfarin use
Protein C or S deficiency
Obesity
Malnutrition or hypoalbuminemia
Diabetes mellitus
Liver disease
Caucasian race
Female sex

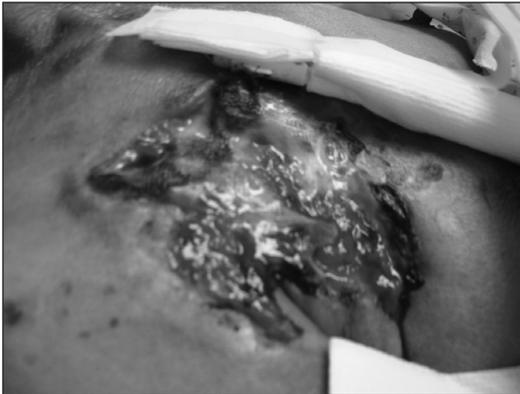


Figure 1. A chest wound characteristic of calcific uremic arteriopathy with (subsequent) growth of granulation tissue.

thiosulfate after approximately two months. The wound was fully healed by the time of manuscript preparation for this report. The patient will again be referred back to the General Surgery Department for parathyroidectomy when her general health and nutritional status improve.

## Conclusion

Our case underscores the need to consider the diagnosis of CUA in patients at high risk. CUA was not initially considered in our patient, probably because the inciting event was bleeding after catheter replacement, and thus the wound was assumed to be a complication of bleeding. The diagnosis of CUA should always be considered when characteristic skin lesions present in a patient who receives dialysis. Diagnosis may be more difficult in the patient without evidence of chronic kidney disease, but if other risk factors are present in conjunction with painful skin lesions, the clinician should always consider the diagnosis of CUA. Although CUA is associated with high morbidity and mortality, early recognition of the disease and a multifaceted approach to treatment may aid in recovery. ❖

## Disclosure Statement

*The author(s) have no conflicts of interest to disclose.*

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